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U. S. Department of Commerce Patent and Trademark Office

ATTORNEY'S DOCKET NUMBER

4-30972A

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

10/009009

INTERNATIONAL APPLICATION NO.
PCT/EP 00/05059INTERNATIONAL FILING DATE
02 June 2000 (02.06.2000)PRIORITY DATE CLAIMED
4 June 1999 (04.06.99)TITLE OF INVENTION
BRADYKININ RECEPTOR ANTAGONISTSAPPLICANT(S) FOR DO/EO/US
BRAIN ET AL.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau. (See Form PCT/IB/308)
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An unexecuted Declaration and Power of Attorney (original or copy) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included.

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment (Abstract).
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☒ Bib Data Sheet
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information: See Form PCT/ISA/210

U.S. APPLICATION NO. (if known, see 37 CFR 1.55)

107/009009

INTERNATIONAL APPLICATION NO.

PCT/EP 00/05059

ATTORNEY'S DOCKET NUMBER

4-30972A

17. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):**

Search Report has been prepared by the EPO or JPO \$890

International preliminary examination fee paid to USPTO (37 CFR 1.482) \$710

No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)). \$740

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO. \$1,040

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4). \$100

CALCULATIONS PTO USE ONLY**ENTER APPROPRIATE BASIC FEE AMOUNT =**

\$ 890

Surcharge of \$130 for furnishing the oath of declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).

\$

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	11	- 20 =	0
Independent claims	3	- 3 =	0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+
			\$ 280

\$

TOTAL OF ABOVE CALCULATIONS =

\$ 890

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).

\$

SUBTOTAL =

\$ 890

Processing fee of \$130 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).

\$

TOTAL NATIONAL FEE =

\$ 890

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property

\$

TOTAL FEES ENCLOSED =

\$ 890

Amount to be:
refunded \$
charged \$

- a. ☐ A check in the amount of \$ _____ to cover the above fees is enclosed.
- b. ☒ Please charge Deposit Account No. 19-0134 in the name of Novartis Corporation in the amount of \$890 to cover the above fees. A duplicate copy of this form is enclosed.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0134 in the name of Novartis Corporation.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

Send all correspondence to the address associated with Customer No. 001095, which is currently:

Thomas Hoxie
Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027

Carol A. Loeschorn
Carol A. Loeschorn
Attorney for Applicants
Reg. No. 35,590
(908) 522-6932

10/009009

JUN 18 2001 PCT/PTC 03 DEC 2001

CASE 4-30972A

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231

Oksana Sporniak
Type or print name

Oksana Sporniak
Signature

11/30/2001
Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE PCT APPLICATION IN THE NATIONAL PHASE OF
BRAIN ET AL.

INTERNATIONAL APPLICATION NO: PCT/EP00/05059

INTERNATIONAL FILING DATE: 2 June 2000

FOR: BRADYKININ RECEPTOR ANTAGONISTS

Assistant Commissioner for Patents
Washington, D.C. 20231

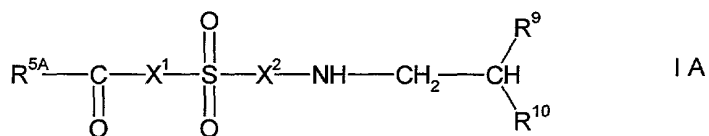
PRELIMINARY AMENDMENT

Sir:

Please amend the subject application by adding the following page as new page 30:

Abstract

Novel sulfonyl amine derivatives, of formula IA processes for their production, their use as pharmaceuticals and pharmaceutical compositions comprising them.



REMARKS

Please make of record the appended abstract, which is being submitted because the published international application lacked an abstract.

Respectfully submitted,

Novartis Corporation
Patent and Trademark Dept.
564 Morris Avenue
Summit, NJ 07901-1027
(908) 522-6932

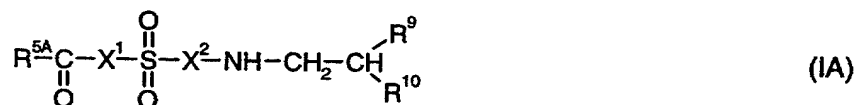

Carol A. Loeschorn
Attorney for Applicants
Reg. No. 35,590

Date: *November 30, 2001*

Bradykinin receptor antagonists

The present invention relates to novel sulfonyl amine derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a compound of formula IA



wherein

R^{5A} is $-\text{X}^A-\text{R}^{6A}$ or $-\text{N}(\text{R}^{7A})\text{R}^{8A}$, wherein

X^A is piperidinylene or piperazinylene,

R^{6A} is H, C_1 - C_4 alkyl, C_3 - C_4 alkenyl, C_3 - C_4 alkinyl, C_1 - C_4 (alkoxyalkyl), C_1 - C_4 (carboxyalkyl), a C_5 - C_7 heterocyclic group or phenyl- C_1 - C_4 alkyl;

R^{7A} is amino- C_2 - C_4 alkyl or mono- or di- $(\text{C}_1$ - C_5 alkyl)amino- C_2 - C_5 alkyl, and

R^{8A} is H, C_1 - C_4 alkyl or has the meanings as given for R^{7A} ;

X^1 is a divalent group of formula IA' $-(\text{CH}_2)_n-\text{X}^3-\text{R}^{4A}-\text{X}^4-\text{N}(\text{R}^{3A})-$ wherein

n is zero or 1;

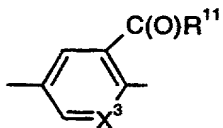
X^3 is CH or N;

(a) X^4 is a direct bond, R^{3A} and R^{4A} together are ethylene and m is 2; or

(b) X^4 is a direct bond, R^{3A} is H, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkinyl, C_7 - C_{10} aralkyl or C_6 - C_9 heteroaralkyl, R^{4A} is H and m is 1 or 2 or 3; or

(c) X^4 is $-\text{CH}(\text{R}^{12})-$, R^{3A} is H and R^{4A} and R^{12} together are propylene and m is 1, or ethylene and m is 2;

X^2 is a divalent group of formula IA''



wherein

X^3 is CH or N; and

R^{11} is C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl or $-\text{NR}^{1A}\text{R}^{2A}$, wherein

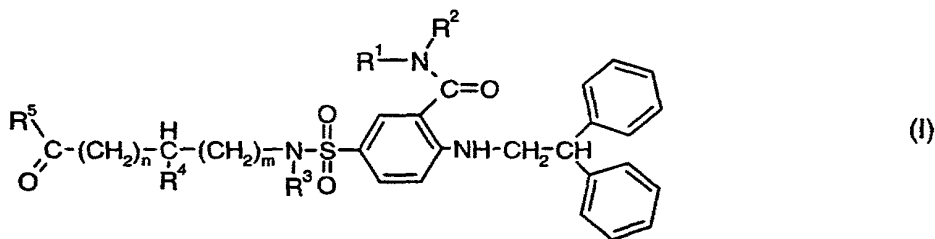
R^{1A} and R^{2A} independently are C_1 - C_4 alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring; and

R^9 and R^{10} independently are a phenyl or pyridine ring;
and salts thereof.

It will be understood that the above defined compounds may bear substituents within their structure, e.g. may bear appropriate phenyl ring or alkylene moiety substituents, e.g. phenyl and pyridine in the meaning of R^9 or R^{10} may be unsubstituted or substituted by one or more halogen, and in the meaning of R^{3A} alkyl may be unsubstituted or substituted by halogen, C_3 - C_6 cycloalkyl or aryl; aralkyl may be unsubstituted or substituted by halogen, methoxy, nitro or C_1 - C_4 alkyl which may be unsubstituted or substituted by halogen; heteroaralkyl may be unsubstituted or substituted by C_1 - C_4 alkyl. The amino moiety of the defined aminocarbonyl or amide groupings can be any appropriate amino grouping, e.g. cyclic or aliphatic or may bear further substituent groupings.

Even more particularly the present invention provides a 2-(2,2-diphenylethylamino)-5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbonyl- C_2 - C_4 alkyleneaminosulfonyl)-benzoic acid amide, or salt thereof.

Preferred compounds in accordance with the invention are those of formula I



wherein

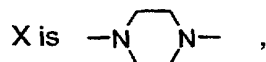
R^1 and R^2 independently are C_1 - C_4 alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring;

(a) R^3 and R^4 together are ethylene and m is 2; or

(b) R^3 is H, C_1 - C_4 alkyl, C_5 - C_7 cycloalkyl or phenyl- C_1 - C_4 alkyl, R^4 is H and m is 1 or 2 or 3;

n is zero or 1; and

R^5 is $-X-R^6$ or $-N(R^7)R^8$, wherein



R⁶ is C₁-C₄alkyl, C₃-C₄alkenyl, C₃-C₄alkinyl, C₁-C₄(alkoxyalkyl), C₁-C₄(carboxyalkyl), a C₅-C₇heterocyclic group or phenyl-C₁-C₄alkyl;

R⁷ is amino-C₂-C₄alkyl or mono- or di-(C₁-C₅alkyl)amino-C₂-C₅alkyl, and

R⁸ is H, C₁-C₄alkyl or has the meanings as given for R⁷;

and salts thereof.

Alkyl groups and moieties in the compounds of formula IA or I may be branched or straight chain. Alkyl groups are suitably straight chain.

Heterocyclic groups may be saturated or unsaturated and may contain one or more additional heterocyclic atoms, e.g. oxygen or sulfur. Examples include piperidin-1-yl, morpholin-1-yl, 3,6-dihydro-2H-pyridin-1-yl, thiomorpholin-1-yl, pyrrolin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, 3,6-dihydro-2H-pyridin-1-yl, 2,5-dihydropyrrol-1-yl and 4-difluoropiperidin-1-yl, and may be unsubstituted or substituted by one or two halogen atoms.

Compounds of the invention exist in free or salt, e.g. acid addition salt form. The invention is to be understood as including both the compounds of formula IA or I in free as well as in salt form, e.g. as trifluoroacetate or hydrochloride salt. Suitable pharmaceutically acceptable acid addition salts for pharmaceutical use in accordance with the invention include in particular the hydrochloride salt.

In formula IA the following significances are preferred independently, collectively or in any combination or sub-combination:

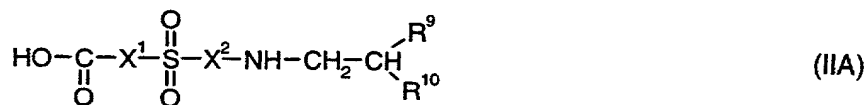
- (a') R^{5A} is unsubstituted piperazinyl or piperazinyl substituted by methyl, ethyl, benzyl, 2-pyridinyl, methoxyethyl, carboxymethyl or -CH₂CHCH₂; or piperidine substituted by methyl;
- (a'') R^{5A} is N(R^{7A})R^{8A} wherein R^{7A} is aminopropyl, aminobutyl, dimethylaminopropyl, diethylaminopropyl, dibutylaminoethyl, dimethylaminobutyl, or dimethylaminopentyl; and R^{8A} is H, methyl, aminopropyl, aminobutyl, dimethylaminopropyl or dimethylaminobutyl;
- (b') X¹ is -(CH₂)_n-CH(R^{4A})-(CH₂)₂-N(R^{3A})- wherein n is zero or 1 and R^{3A} and R^{4A} together are ethylene;

- (b'') X^1 is $-\text{CH}(\text{R}^{4A})-(\text{CH}_2)_m-\text{CH}(\text{R}^{12})-\text{NH}-$ wherein m is 1 or 2 and R^{4A} and R^{12} together are propylene or ethylene;
- (b''') X^1 is $-(\text{CH}_2)_n-\text{CH}_2-(\text{CH}_2)_m-\text{N}(\text{R}^{3A})-$ wherein n is zero or 1, m is 1 or 2 or 3 and R^{3A} is H, methyl, isopropyl, isobutyl, fluoroethyl, cyclopropylmethyl, cyclohexylmethyl, cyclobutylmethyl, $-\text{CH}(\text{CH}_3)\text{C}_6\text{H}_5$, cyclohexyl, propenyl, butenyl, pentenyl, propinyl, butinyl, pentinyl, benzyl, methylbenzyl, fluorobenzyl, trifluoromethylbenzyl, methoxybenzyl, nitrobenzyl, pyridinylmethyl, methylisoxazolylmethyl, methylthiazolylmethyl or thiophenemethyl;
- (c') X^2 is a divalent group of formula IA'' wherein X^3 is CH and R^{11} is methyl, cyclopentyl, cyclohexyl, $\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_3$, piperidiny, morpholinyl, thiomorpholinyl, dihydropyridinyl, dihydropyrrolyl or difluoropiperidiny;
- (c'') X^2 is a divalent group of formula IA'' wherein X^3 is N and R^{11} is morpholinyl;
- (d) R^9 and R^{10} are phenyl which is unsubstituted or substituted by halogen;
- (d'') R^9 is phenyl and R^{10} is pyridine.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination:

- (a¹) R^1 and R^2 are independently methyl or ethyl.
- (a²) R^1 and R^2 together with the N-atom to which they are attached are piperidin-1-yl, morpholin-1-yl, 3,6-dihydro-2.H.pyridin-1-yl, thiomorpholin-1-yl or pyrrolin-1-yl.
- (b¹) R^3 and R^4 together are ethylene and m is 2.
- (b²) R^3 is H, methyl, cyclohexyl or benzyl; R^4 is H and m is 1 or 2 or 3, especially 1.
- (c) n is zero or 1.
- (d¹) R^5 is $-\text{X}-\text{R}^6$, wherein R^6 is C_1 - C_4 alkyl (e.g. methyl, ethyl or isopropyl), 3-propenyl, methoxyethyl, carboxymethyl, 2-pyridyl, or benzyl, and X is as defined above.
- (d²) R^5 is $-\text{N}(\text{R}^7)\text{R}^8$, wherein R^7 is aminopropyl, aminobutyl, dipropylaminoethyl, dimethylaminopropyl, dimethylaminobutyl, diethylaminopropyl or dimethylaminopentyl; and R^8 is H, methyl, aminopropyl, aminobutyl, dimethylaminopropyl or dimethylaminobutyl.

In addition to the foregoing the present invention also provides a process for the production of a compound of formula IA which process comprises reacting a compound of formula IIA

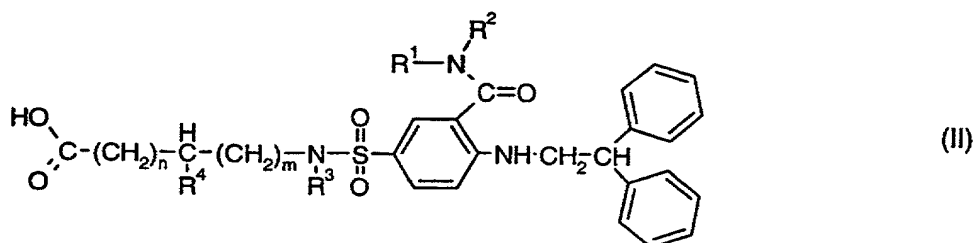


wherein X^1 , X^2 , R^9 and R^{10} have the meanings given for formula IA,
with an amine, e.g. of formula IIIA



wherein R^{5A} has the meanings given for formula IA,
and recovering the obtained compound, e.g. of formula IA, in free or in salt form, e.g. acid
addition salt form.

The present invention also provides a process for the production of a 2-(2,2-diphenylethyl-
amino)- 5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbon-
yl- C_{2-4} alkylene aminosulfonyl)-benzoic acid amide, for example a compound of formula I as
defined above, or salt thereof, which process comprises reacting a 2-(2,2-diphenylethylamino)-
-5-(4-carboxy-piperidine-1-sulfonyl)-benzoic acid amide or -5-(carboxy- C_{2-4} alkylene
aminosulfonyl)-benzoic acid amide, for example a compound of formula II



wherein R^1 , R^2 , R^3 , R^4 , m and n have the meanings given for formula I,
with an amine, e.g. of formula III



wherein R^5 has the meanings given for formula I,
and recovering the obtained compound, e.g. of formula I, in free or in salt form, e.g. acid
addition salt form.

The reaction may be carried out in accordance with standard procedures, for example by a first
acid chloride formation step using e.g. thionyl chloride and catalytic DMF in an inert solvent, e.g.
 CH_2Cl_2 , at ambient temperature, followed by the coupling step involving addition of the acid
chloride to a mixture of the amine and e.g. TEA, at a temperature of, e.g. -10°C . Aqueous

workup followed by precipitation from, e.g. ethyl acetate gives the free base. The salt forms are made by standard procedures known to the skilled artisan.

In the examples the following abbreviations are used: DMF: dimethyl formamide; DMSO: dimethyl sulfoxide; EDTA: ethylenediamine-tetraacetic acid; EtOAc: ethylacetate; IPA: isopropanol; RT: room temperature; TBME: t-butyl methyl ether; TBTU: (O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate; TEA: triethylamine; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

Example 1: Preparation of {2-(2,2-diphenyl-ethylamino)-5-[4-(4-isopropyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone
(formula I: $R^1 + R^2 + N = \text{morpholin-4-yl}$, $R^3 + R^4 = \text{ethylene}$, $m = 2$, $n = \text{zero}$, $R^5 = 4\text{-isopropyl-piperazin-1-yl}$)

(a) A 5 liter flask is charged with {2-(2,2-diphenyl-ethylamino)-5-[4-(4-carboxy)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone (130.2 g), CH_2Cl_2 (1.3 l), DMF (0.82 g) and thionyl chloride (18.1 ml, 29.51 g). The suspension is stirred at ambient temperature (the solids dissolved after ~2 h). The volatiles are removed by rotary evaporation (30°C, house vacuum) and the crude acid chloride is redissolved in CH_2Cl_2 (300 ml). The solution of acid chloride is added to a mixture of isopropylpiperazine (47.60 g), TEA (98.09 g) and CH_2Cl_2 (1 l) at -10°C over 1 h. The reaction is worked up by removing volatiles via rotary evaporation. The residue is suspended in EtOAc (2.0 l) and washed with water (2 x 500 ml), brine (500 ml) and dried (Na_2SO_4). The volume is reduced by rotary evaporation (35°C, house vacuum) to ~500 ml and stirred at ambient temperature for 17 h. The suspension is filtered and dried (40°C, house vacuum) to give the title compound as free base.

(b) A 5 liter flask is charged with the above compound (121.3 g), CH_2Cl_2 (1.2 l), and 37 % HCl (17.38 g). After stirring for 30 min, the volatiles are removed by rotary evaporation and the residue is triturated with IPA (1 l). The suspension is filtered and dried (40°C, house vacuum) to give the crude HCl salt of the title compound.

(c) A 2 liter flask is charged with the above crude HCl salt (133.7 g), silica gel (13.0 g) and CH_2Cl_2 (1.3 l). The mixture is stirred for 15 min at ambient temperature and then filtered. This process is repeated twice more. The solvent is removed by rotary evaporation. The residue is suspended in a mixture of IPA (1.0 l) and water (100 ml) and heated to reflux. The solution is allowed to cool to ambient temperature and stir for 17 h. The resulting sus-

pension is filtered and dried. The solid is suspended in acetone (1.0 l) and refluxed for 4.5 h. The suspension is cooled to ambient temperature and stirred for 3 days. The suspension is filtered and dried (60°C, house vacuum, 2 days) to give the title compound as HCl salt.

In the following examples compounds of formula IA wherein R^{3A} and R^{4A} together are ethylene, m is 2, X^3 is CH and R^{5A} is $-X^A-R^{6A}$ wherein X^A is piperazin-1,4-ylene, are prepared analogously to Example 1:

Example	R^{11}	n	R^{6A}	R^9/R^{10}
2*	morpholin-4-yl	0	-CH ₃	phenyl
3*	3,6-dihydro-2H-pyridin-1-yl	0	-CH ₃	phenyl
4	piperidin-1-yl	0	-CH ₃	phenyl
5*	morpholin-4-yl	0	-CH ₂ CH ₃	phenyl
6	thiomorpholin-4-yl	0	-CH ₃	phenyl
7*	morpholin-4-yl	0	benzyl	phenyl
8	-N(CH ₃)CH ₂ CH ₃	0	-CH ₃	phenyl
9*	morpholin-4-yl	0	-CH ₂ CHCH ₂	phenyl
10*	morpholin-4-yl	0	-CH ₂ CH ₂ OCH ₃	phenyl
11*	3,6-dihydro-2H-pyridin-1-yl	0	-CH(CH ₃)CH ₃	phenyl
12*	morpholin-4-yl	0	2-pyridinyl	phenyl
13	2,5-dihydropyrrol-1-yl	0	-CH ₃	phenyl
14	3,6-dihydro-2H-pyridin-1-yl	1	-CH ₃	phenyl
15	morpholin-4-yl	0	-CH ₂ C(O)OH	phenyl
1.1	morpholin-4-yl	1	-CH ₃	phenyl
1.2	-CH ₃	0	-CH ₃	phenyl
1.3	morpholin-4-yl	0	-CH ₃	4-Cl-phenyl
1.4	-C ₅ H ₉	0	-CH ₃	phenyl
1.5	-C ₆ H ₁₁	0	-CH ₃	phenyl
1.6	morpholin-4-yl	0	-CH ₃	4-F-phenyl
1.7	4-difluoropiperidin-1-yl	0	-CH ₃	phenyl
1.8	morpholin-4-yl	0	-H	phenyl

* as trifluoroacetate

In the following examples compounds of formula I wherein R^3 and R^4 together are ethylene, m is 2 and R^5 is $-N(R^7)R^8$ are prepared analogously to Example 1:

Example	$-NR^1R^2$	n	R^7	R^8
16	3,6-dihydro-2H-pyridin-1-yl	0	$-(CH_2)_3N(CH_3)_2$	$-(CH_2)_3N(CH_3)_2$
17	morpholin-4-yl	0	$-(CH_2)_4NH_2$	$-(CH_2)_3NH_2$
18	morpholin-4-yl	0	$-(CH_2)_3N(CH_3)_2$	$-(CH_2)_4N(CH_3)_2$
19	morpholin-4-yl	0	$-(CH_2)_3N(CH_3)_2$	$-CH_3$
20	morpholin-4-yl	0	$-(CH_2)_3N(CH_2CH_3)_2$	$-H$
21	morpholin-4-yl	0	$-(CH_2)_2N[(CH_2CH(CH_3)_2)_2]$	$-H$
22	morpholin-4-yl	0	$-CH_2C(CH_3)_2CH_2N(CH_3)_2$	$-H$

In the following examples compounds of formula IA wherein n is 0, m is 2, X^4 is a direct bond, R^{3A} and R^{4A} together are ethylene and R^{11} is morpholin-4-yl are prepared analogously to Example 1:

Example	R^{5A}	X^3	X^5	R^9	R^{10}
3.1	4-methylpiperazin-1-yl	N	C	phenyl	phenyl
3.2	4-methylpiperazin-1-yl	C	N	phenyl	phenyl
3.3	1-methyl-piperidin-4-yl	N	C	phenyl	phenyl
3.4	4-methylpiperazin-1-yl	C	C	phenyl	pyridine

In the following examples compounds of formula IA wherein R^{3A} is H, R^{5A} is 4-methylpiperazin-1-yl, R^9 and R^{10} are phenyl, R^{11} is morpholin-4-yl, n is 0, X^3 and X^5 are CH and X^4 is $-CH(R^{12})-$ are prepared analogously to Example 1:

Example	$R^{4A} + R^{12}$ together	m
4.1	propylene	1
4.2	ethylene	2

In the following examples compounds of formula IA wherein R^{1A} and R^{2A} together with the N-atom to which they are attached are morpholin-4-yl, R^{4A} is H and R^{5A} is $-X^A-R^{6A}$ wherein X^A is piperazin-1,4-ylene, are prepared analogously to Example 1:

Example	R ^{3A}	m	n	R ^{6A}
23	-CH ₃	1	1	-CH ₃
24*	-CH ₃	1	1	-CH(CH ₃)CH ₃
25*	benzyl	1	0	-CH ₃
26*	cyclohexyl	1	0	-CH ₃
27*	-CH ₃	1	0	-CH(CH ₃)CH ₃
28*	benzyl	1	1	-CH(CH ₃)CH ₃
29	-H	2	1	-CH(CH ₃)CH ₃
30	-CH ₃	3	1	-CH ₃
5.1	-CH ₂ C ₃ H ₅	2	0	-CH ₃
5.2	2-methylbenzyl	2	0	-CH ₃
5.3	2-fluorobenzyl	2	0	-CH ₃
5.4	3-methylbenzyl	2	0	-CH ₃
5.5	3-fluorobenzyl	2	0	-CH ₃
5.6	4-methylbenzyl	2	0	-CH ₃
5.7	4-fluorobenzyl	2	0	-CH ₃
5.8	-CH ₂ CH ₂ F	2	0	-CH ₃
5.9	-CH(CH ₃)C ₆ H ₅	2	0	-CH ₃
5.10	-CH ₂ CH(CH ₃) ₂	2	0	-CH ₃
5.11	-CH ₂ C(CH ₃)CH ₃	2	0	-CH ₃
5.12	2-trifluoromethylbenzyl	2	0	-CH ₃
5.13	3-trifluoromethylbenzyl	2	0	-CH ₃
5.14	4-trifluoromethylbenzyl	2	0	-CH ₃
5.15	3-methoxybenzyl	2	0	-CH ₃
5.16	4-methoxybenzyl	2	0	-CH ₃
5.17	2-nitrobenzyl	2	0	-CH ₃
5.18	3-nitrobenzyl	2	0	-CH ₃
5.19	pyridin-3-ylmethyl	2	0	-CH ₃
5.20	pyridin-4-ylmethyl	2	0	-CH ₃
5.21	-CH ₂ CHCH ₂	2	0	-CH ₃
5.22	-CH ₂ CCH	2	0	-CH ₃

Compound	R ^{3A}	m	n	R ^{6A}
5.23	5-methylisoxazol-3-ylmethyl	2	0	-CH ₃
5.24	2-methylthiazol-4-ylmethyl	2	0	-CH ₃
5.25	-CH ₂ CHC(CH ₃) ₂	2	0	-CH ₃
5.26	-CH ₂ CHCHCH ₃	2	0	-CH ₃
5.27	-CH ₂ C ₆ H ₁₁	2	0	-CH ₃
5.28	-CH ₂ C ₄ H ₇	2	0	-CH ₃
5.29	-CH ₂ CCCH ₃	2	0	-CH ₃
5.30	thiophen-3-ylmethyl	2	0	-CH ₃
5.31	thiophen-2-ylmethyl	2	0	-CH ₃
5.32	-CH ₂ CCCH ₂ CH ₃	2	0	-CH ₃
5.33	-CH(CH ₃) ₂	2	0	-CH ₃

CHARACTERISING DATA

Compounds of the above tables are found to exhibit the following HPLC retention data [min]:

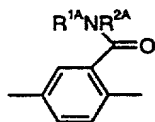
No	[min]	No	[min]	No	[min]	No	[min]
1	5.91*	15	7.17****	26	24.95***	35	6.083*
2	5.68*	16	5.0*****	27	5.90*	36	6.100*
3	6.22*	17	5.7*****	28	6.23*	37	6.067*
4	5.43**	18	24.03***	29	5.35*	38	5.967*
5	23.55***	19	4.6*****	30	5.75*	39	4.767*
6	5.24**	20	20.1***	31	5.833*	40	4.667*
7	25.93***	21	22.6***	32	6.367*	41	5.567*
8	5.09**	22	22.58***	33	6.100*	42	6.02*
9	23.98***	23	27.57***	34	6.250*	43	6.138*
10	23.89***	24	22.9***	35	6.167*	44	6.087*
11	6.37*	25	5.03*****	36	6.45*	45	6.558*
12	23.68***	26	5.8*	37	6.200*	46	6.382*
13	5.10**	27	5.83*	38	5.467	47	6.932*
14	6.17****	28	3.4*****	39	6.167*	48	6.547*
15	5.28****	29	5.467*	40	5.900*	49	6.26*
16	4.95*****	30	5.822*	41	6.338*	50	6.453*

No.	[min]	No.	[min]	No.	[min]	No.	[min]
1.2	6.00****	23	5.57*	5.12	6.998*	5.3	5.7*****
1.3	6.4****	24	5.9*	5.13	6.983*	5.31	5.7*****
1.4	6.82****	25	23.82***	5.14	7.03*	5.33	6.510*

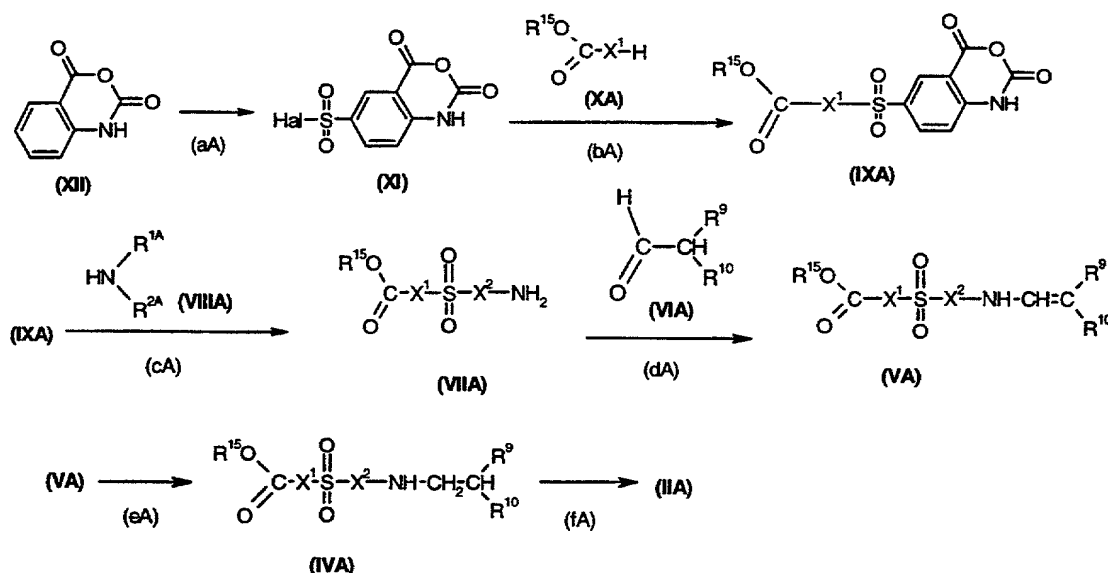
HPLC conditions:

- *: Hypersil 3 micron C 18 BDS column. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 10 min
- ** : Kingsorb 50x4.6mm C18 column, 3micron particle size; flow rate 3ml/min; 90% water (+10mM NH₄OAc 0.3% HCOOH) 10% MeCN to 100% MeCN over 10min
- ***: Nucleosil 5 micron C18 column, 25cm x 4.6mm. Gradient elution 10-100% MeCN in water (+0.1% TFA) over 40 min
- ****: Waters Symmetry 3 micron C18 column; 5 x 0.46 cm. Gradient elution, 10% to 100% MeCN in water (+ 0.1% TFA) over 10 min
- *****: Kingsorb 3 micron C18 column, 30x4.6mm, gradient elution 10 % MeCN in water (+0.1% TFA) to 100% MeCN over 10 min

Compounds of formula IIA wherein X¹, R⁹ and R¹⁰ have the above meanings and X² is a divalent group of formula



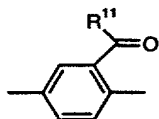
wherein R^{1A} and R^{2A} independently are C₁-C₄alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring,
may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:



wherein Hal is halogen, e.g. chlorine, R¹⁵ is C₁-C₄alkyl, e.g. ethyl, and X¹, X², R^{1A}, R^{2A}, R⁹ and R¹⁰ are as defined for formula IA.

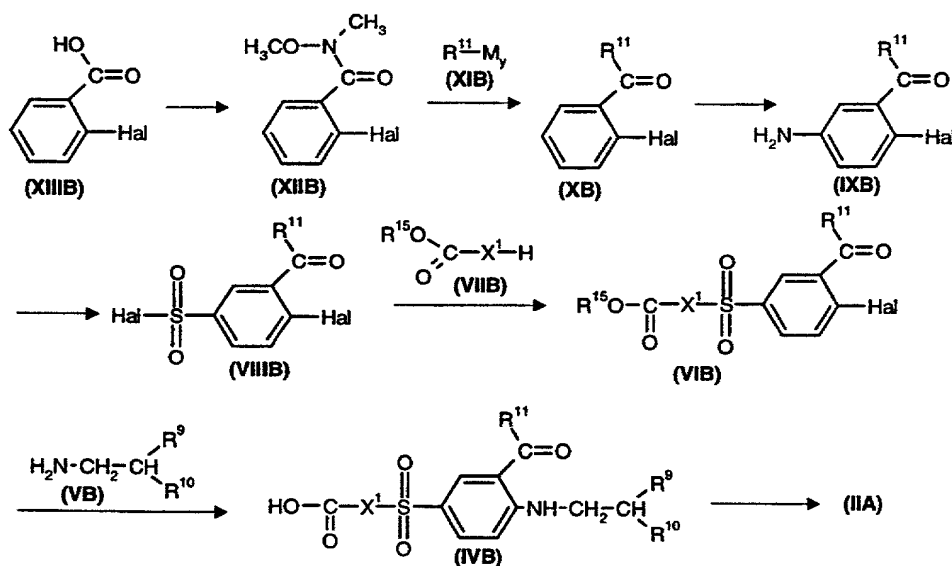
Each of the above reaction steps may be carried out in accordance with conventional procedures as known in the art, e.g. as illustrated in the following examples or analogously thereto. For example in step (aA) the compound of formula XIIA may conveniently be reacted with e.g. chlorosulfonic acid or with chlorosulfonic acid followed by thionyl chloride. In step (bA) the compound of formula XIA may be reacted with the compound of formula XA and e.g. triethylamine in the presence of a solvent like acetonitrile and acetone at 0°C. In step (cA) the compound of formula IXA may be reacted with the compound of formula VIII A at room temperature in the presence of a solvent like acetonitrile, acetone or ethyl acetate, ethyl acetate being preferred. Preferably an excess of the compound of formula VIII A may be used, e.g. a 10 % excess. In step (dA) the compound of formula VIIA may be reacted with an excess of the compound of formula VIA, e.g. a 10 % excess, in the presence of, e.g. trifluoroacetic acid and a desiccant, e.g. trimethyl orthoacetate. The reduction of step (eA) may, e.g. be accomplished via hydrogenation over 10 % palladium on carbon in the presence of a solvent, e.g. tetrahydrofuran. The hydrolysis of the ester of formula IVA [step (fA)] may be accomplished in the presence of a base like NaOH, in a solvent like ethanol, methanol, acetone or tetrahydrofuran, preferably tetrahydrofuran. In some of the above steps the reactants may be warmed prior to reaction.

Compounds of formula IIA wherein X^1 , R^9 and R^{10} have the above meanings and X^2 is a divalent group of formula



wherein R^{11} is C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl,

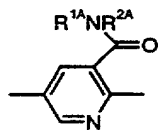
may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:



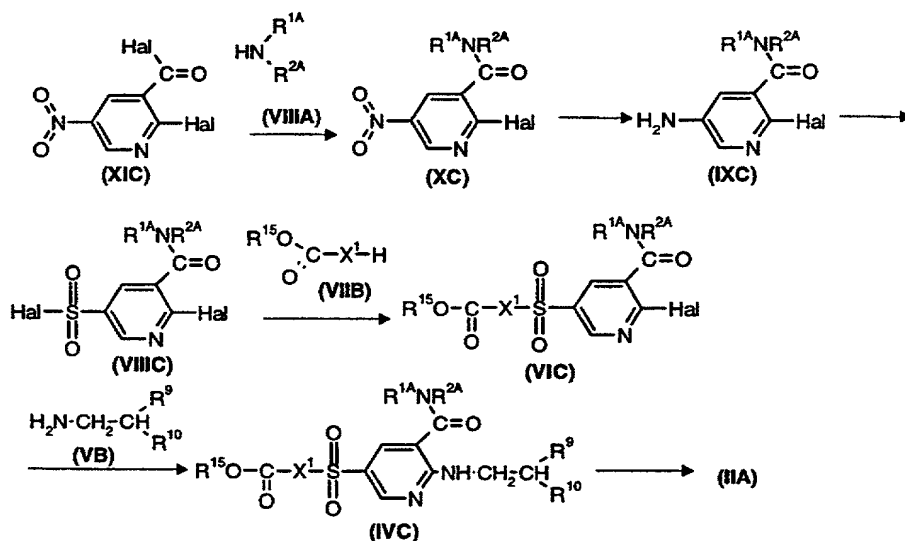
wherein Hal is halogen, e.g. chlorine, R^{15} is C_1 - C_4 alkyl, e.g. ethyl, y is 1 and M is a monovalent metal or y is 1/2 and M is a divalent metal, and X^1 , R^9 , R^{10} and R^{11} are as defined for formula IA.

Examples of a metal include an alkali metal, e.g. lithium (Li), sodium (Na) and potassium (K), an alkaline earth metal, e.g. magnesium (Mg), or manganese (Mn), iron (Fe), zinc (Zn) or silver (Ag).

Compounds of formula IIA wherein X^1 , R^9 and R^{10} have the above meanings and X^2 is a divalent group of formula

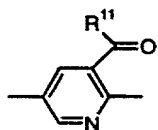


wherein R^{1A} and R^{2A} independently are C_1 - C_4 alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring, may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:

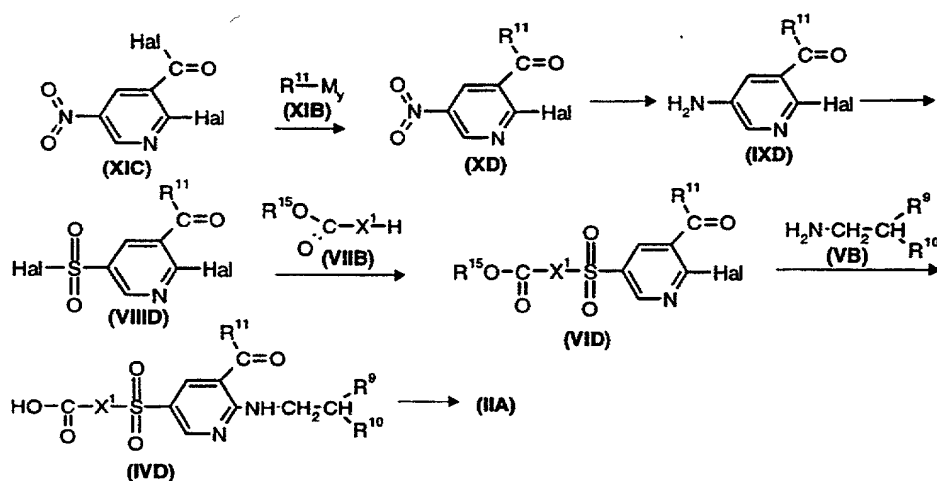


wherein Hal is halogen, e.g. chlorine, R^{15} is C_1 - C_4 alkyl, e.g. ethyl, and X^1 , R^{1A} , R^{2A} , R^9 and R^{10} are as defined for formula IA.

Compounds of formula VIIA wherein X^1 , R^9 and R^{10} have the above meanings and X^2 is a divalent group of formula

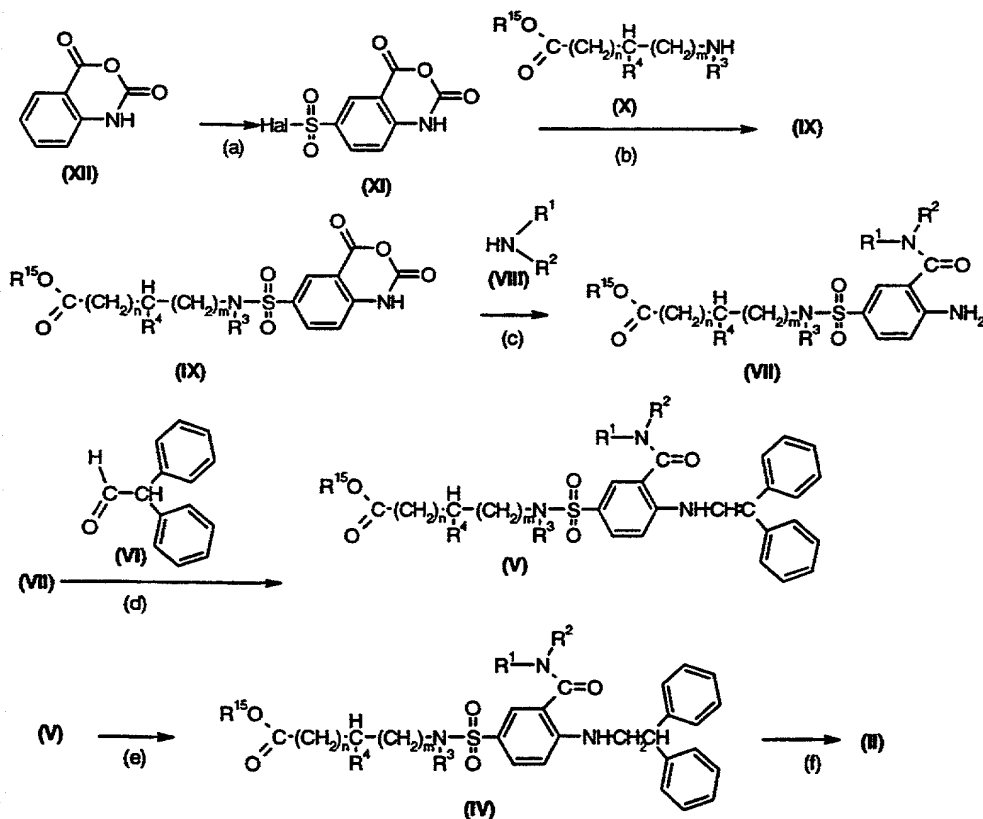


wherein R^{11} is C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:



wherein Hal is halogen, e.g. Cl, R^{15} is C_1 - C_4 alkyl, e.g. ethyl, y is 1 and M is a monovalent metal or y is 1/2 and M is a divalent metal, and X^1 , R^9 , R^{10} and R^{11} are as defined for formula IA.

Compounds of formula II may be prepared applying known techniques, e.g. in accordance with the following reaction scheme:



wherein Hal is halogen, e.g. chlorine, R^{15} is C_1 - C_4 alkyl, e.g. ethyl, and R^1 , R^2 , R^3 , R^4 , m and n are as defined for formula I.

Each of the above reaction steps may be carried out in accordance with conventional procedures as known in the art, e.g. as illustrated in the following examples or analogously thereto. For example in step (a) the compound of formula XII may conveniently be reacted with e.g. chlorosulfonic acid or with chlorosulfonic acid followed by thionyl chloride. In step (b) the compound of formula XI is reacted with the compound of formula X and e.g. triethylamine in the presence of a solvent like acetonitrile and acetone at 0°C . In step (c) the sulfonamide of formula IX is reacted with the compound of formula VIII at room temperature in the presence of a solvent like acetonitrile, acetone or ethyl acetate, ethyl acetate being preferred. Preferably an excess of the compound of formula VIII may be used, e.g. a 10 % excess. In step (d) the compound of formula VII may be reacted with an excess of the compound of formula VI, e.g. a 10 % excess, in the presence of, e.g. trifluoroacetic acid and a desiccant, e.g. trimethyl orthoacetate. The reduction of step (e) may for example be accomplished via hydrogenation over 10 % palladium on carbon in the presence of a solvent, e.g. tetrahydrofuran. The hydrolysis of the ester of formula IV [step (f)] may be accomplished in the presence of a base like NaOH, in a solvent like ethanol, methanol, acetone or tetrahydrofuran, preferably tetrahydrofuran. In some of the above steps the reactants may be warmed prior to reaction.

Starting compounds of formula IIIA, VB, VIA, VIB, VIC, VID, VIIB, VIIIA, XA, XIB, XIC and XIIB are known or may be prepared from corresponding known compounds. Starting compounds III, VI, VIII, X and XII are known or may be prepared from corresponding known compounds.

Example S1: Preparation of {2-(2,2-diphenyl-ethylamino)-5-[4-(4-carboxy)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone (formula II: $R^1 + R^2 + N =$ morpholin-4-yl, $R^3 + R^4 =$ ethylene, $m = 2$, $n = \text{zero}$)

(a) A 2 liter flask is charged with isatoic anhydride (180.3 g) and chlorosulfonic acid (367 ml, 643.9 g). The mixture is stirred at ambient temperature for 21 h. Thionyl chloride (80.6 ml, 131.5 g) is added over 2 h and the mixture is stirred at ambient temperature for 16 h. The reaction is worked up by slowly pouring the reaction mixture over ice (4.5 kg) with stirring. The resulting suspension is filtered and the filtercake is washed with water (2 x 500 ml). The solid is dried (40°C , house vacuum, 48 h) to give compound 2.

(b) A 5 liter flask is charged with 2 (270.2 g) and acetone (2.0 l). The suspension is cooled in an ice/methanol bath and a solution of ethyl isonipecotate (165.7 g) and TEA (156.8 g) in acetone (700 ml) is added over 1.43 h. After the addition is complete, the cooling bath is removed and the mixture is stirred for 2 h. The reaction is worked up by removing volatiles via rotary evaporation (35°C, house vacuum). The solid is triturated with 0.5 N HCl (1763 ml). The suspension is filtered and the filtercake is washed with water (1.0 l). The solid is dried (40°C, house vacuum, 3 days) to give compound 4.

(c) A 12 liter flask is charged with 4 (342.4 g) and EtOAc (3.4 l). A solution of morpholine (85.80 g) in EtOAc (340 ml) is added at ambient temperature over 1.5 h. The mixture is stirred for 30 min. The reaction is worked up by adding charcoal (35.2 g) and filtering through Celite. The solids are washed with EtOAc and the filtrate is reduced to ~2 l by rotary evaporation. Heptane (1.7 l) is added at ambient temperature over 2 h and the resulting suspension is stirred overnight. The suspension is filtered, washed with mother liquor, and dried overnight (40°C, house vacuum) to give 6.

(d) A 12 liter flask is charged with compound 6 (324.7 g) and EtOAc (4.4 l). The mixture is heated until all of the solids dissolved (~35°C). 2,2-diphenyl ethanal (164.7 g), trimethyl orthoacetate (100.8 g), and TFA (4.35 g) are added and the mixture is stirred at ambient temperature for 3 days. The reaction is worked up by removing EtOAc via rotary evaporator. The residue is triturated with TBME (3.2 l). The resulting suspension is filtered, the filtercake is washed with TBME (320 ml) and dried (40°C, house vacuum, N₂ purge) to give compound 8.

(e) A 2.5 liter Parr bottle is charged with compound 8 (118.8 g) and THF (1.2 l). The mixture is heated with stirring until all of the solids are dissolved (~55°C). Palladium on carbon (10 %, anhydrous, 10.47 g) is added and the mixture is shaken under a hydrogen atmosphere (50 psi) at ambient temperature for 24 h. The reaction is worked up by filtering the mixture through Celite. THF is removed by rotary evaporator. The residue is triturated with TBME (1.1 l). The resulting suspension is filtered, the filtercake is washed with TBME (110 ml) and dried (40°C, house vacuum, N₂ purge) to give compound 9.

(f) A 12 liter flask is charged with 9 (326.8 g), THF (3.3 l), and 1.0 N NaOH (540 ml). The biphasic solution is stirred at ambient temperature for 24 h. The reaction is worked up by removing THF via rotary evaporator. Water (1.0 l) is added to the remaining aqueous portion and 1.0 N HCl (600 ml) is added with stirring at ambient temperature over 2 h. The

resulting suspension is filtered, the filtercake is washed with water (1 l) and dried (40°C, house vacuum, N₂ purge) to give the title compound.

Compounds of formula II, IV, V, VII and IX are new and also an embodiment of the present invention.

The following examples for compounds of formula IIA wherein R^{3A} and R^{4A} together are ethylene and m is 2 are prepared analogously to Example S1:

Example	-NR ^{1A} R ^{2A}	n
II.3	3,6-dihydro-2H-pyridin-1-yl	0
II.4	piperidin-1-yl	0
II.6	thiomorpholin-4-yl	0
II.8	-N(CH ₃)CH ₂ CH ₃	0
II.13	2,5-dihydropyrrol-1-yl	0
II.14	3,6-dihydro-2H-pyridin-1-yl	1
II.1.7	4-difluoropiperidin-1-yl	0

The following examples for compounds of formula II wherein R¹ and R² together with the N-atom to which they are attached are morpholinyl, and R⁴ is H are prepared analogously to Example S1:

Example	R ³	m	n	Example	R ³	m	n
II.23	-CH ₃	1	1	II.28	benzyl	1	1
II.25	benzyl	1	0	II.29	-H	2	1
II.26	cyclohexyl	1	0	II.30	-CH ₃	3	1
II.27	-CH ₃	1	0				

The compounds of the invention and their pharmaceutically acceptable acid addition salts (hereinafter: Pharmaceutical Compounds) have pharmacological activity and are useful as pharmaceuticals. In particular Pharmaceutical Compounds exhibit bradykinin antagonist activity. In particular Pharmaceutical Compounds, e.g. compounds of Example 1 and 2, are active at the human B₁ bradykinin receptor.

Bradykinin receptor interaction of the Pharmaceutical Compounds is demonstrated by their ability to displace bradykinin at human bradykinin receptor sites, e.g. as demonstrated in accordance with the following test method.

Test I: Bradykinin receptor binding assay

Cloning of the human bradykinin B1 receptor cDNA: The human bradykinin B1 receptor is cloned from WI38 human foetal lung cell fibroblast cells by expression cloning in *Xenopus laevis* oocytes, which do not express bradykinin B1 receptors normally. A cDNA library is prepared in bacteriophage lambda ZAP express and grown in pools of approximately 10,000 clones per pool. Bacteriophage DNA is prepared from these pools and copy RNA is synthesised with T3 RNA polymerase and after phenol extraction and precipitation, the RNA is injected into *Xenopus* oocytes and allowed to be expressed for 3 days. The oocytes are then assayed electrophysiologically using two electrode voltage clamp, for a response in an endogenous chloride channel that can be activated by endogenous heterotrimeric GTP binding proteins of the Gq/G11 type that can couple to bradykinin receptors. A positive clone is isolated from a positive pool by several stages of splitting the pool into smaller pools and assaying, until a single clone is isolated. This cDNA is sequenced and subcloned into pcDNA3 (Clontech) and used to generate a cell-line which expresses the human bradykinin B1 receptor.

Making the HEK cells: The human bradykinin B1 receptor cDNA is subcloned into the Kpn1 and Not1 sites of pcDNA3 (HB1-pcDNA3), is grown up and transfected into human embryonic kidney fibroblast cell line, HEK 293 using the Calcium phosphate method. Cells are grown in Minimum Essential Medium with Earle's Salts (GIBCO) supplemented with 2 mM L-glutamine, 100 units/ml penicillin, 100 µg/ml streptomycin, 1 % nonessential amino acids and 10 % myoclone foetal calf serum (GIBCO) in a humidified atmosphere with 5 % CO₂ at 37°C.

The 293Hek cells are split 1:2 the day prior to transfection. One 175 cm² flask with approximately 50 % confluent cells is transfected with approximately 30 µg/ml HB1-pcDNA3 DNA using the calcium phosphate precipitate method of transfection. The flask of transfected cells is split 1:3 on day 2 post transfection to prevent overgrowth. The following day the cells are split 1:5 and selection in 700 µg/ml G418 begins. The selective medium is changed every 3-4 days. When distinct G418 resistant colonies of transfected cells are seen, approximately 4 weeks after transfection, the cells are cloned by limiting dilution and assayed for binding of [³H]desArg¹⁰-kallidin. The clone with the highest binding is chosen for

further use. Care is taken not to allow the cells to overgrow and to maintain G418 in the growth medium.

These HEK 293 cells expressing the human bradykinin B₁ receptor are used to prepare membranes. Cells are homogenised in 50 mM Tris-HCl, 1 mM EDTA pH 7.4 at 10,000 rpm for 30 sec in a Polytron homogeniser. All subsequent operations are carried out at 4°C. The resultant suspension is centrifuged for 30 min at 28,000 x g. The pellet is washed a further two times by resuspension in Tris-HCl (50 mM, pH 7.4) and recentrifugation. The final pellet is resuspended in Tris-HCl (50 mM, pH 7.4), containing 5 % glycerol and frozen rapidly on dry ice in 500 µl aliquots and stored at -80°C.

For use in the binding assay, membranes are thawed, homogenised, and diluted with physiological binding buffer (10 mM HEPES, HBSS {137 mM NaCl, 5.4 mM KCl, 1.3 mM CaCl₂, 0.4 mM KH₂PO₄, 0.3 mM NaHPO₄, 0.5 mM MgCl₂, 0.4 mM MgSO₄, 5.6 mM glucose, pH 7.4} containing 1 mM 1-10 phenanthroline and 0.14 g/l bacitracin. Binding assays are performed in 1.2 ml polypropylene assay tubes (incorporated into a deep well block of 96 or individual Micronics tubes) containing a final volume of 0.5 ml. The assay composition is 425 µl membrane suspension (approximately 20 µg protein per tube) in physiological binding buffer, 50 µl [³H]desArg¹⁰-kallidin (specific activity 95 Ci/mMol; 6.0 ± 0.5 nM), 25 µl of either DMSO, or unlabelled desArg¹⁰ kallidin (20 µM) or different concentrations of Pharmaceutical Compounds made up in DMSO. Specific binding to the bradykinin B₁ receptor is defined as the difference between that found in total bound tubes and that found in non-specific binding tubes. The reaction is initiated with the addition of membranes and incubated at 4°C for 60 min. The reaction is terminated by rapid filtration of the assay mixture through Canberra Packard Unifilter-96 GF/B filterplates (which have been pre-soaked in 0.6% polyethyleneimine for 2 to 3 h at RT). The filters are washed 4 times with 1 ml aliquots of ice cold wash buffer. Microscintillant-40 liquid scintillant is added to the filters and radioactivity bound is determined in a Canberra Packard Topcount scintillation counter. Binding parameters are derived from non-linear iterative curve fitting of three or four data sets simultaneously, using a logistic model in MicrocalTM Origin.

K_i values are 0.063 µM for the peptide antagonist desArg¹⁰HOE [(D-Arg-[Hyp³, Thi⁵, D-Tic⁷, Oic⁸]desArg⁹ bradykinin) = (D-Arginine-[hydroxyproline³, thienyamine⁵, D-tetrahydroxyquinoline-3-carboxylic acid⁷, octahydroindole-2-carboxylic acid⁸]desArginine⁹ bradykinin)] and in the range of 0.5 nM to 2 µM for Pharmaceutical Compounds.

Activity specifically as analgesic agents may be demonstrated in accordance with standard test methods, e.g. as described in the following test.

Test II: Thermal antinociception in monkeys (warm water tail-withdrawal)

Carrageenan at a dosage of 2 mg in 100 μ l saline is injected subcutaneously into the terminal 1 to 4 cm of the tail of adult rhesus monkeys (*Macaca mulatta*) followed by administration of Pharmaceutical Compound in 100 μ l vehicle (0.5 % methylcellulose in distilled water) or vehicle to the animal.

The animals are seated in restraint chairs and the lower part of the shaved tail (approximately 15 cm) immersed into warm water maintained at temperatures of 42, 46, and 50°C. Tail-withdrawal latencies are recorded manually by a computerized timer. A maximum cutoff latency (20 sec) is recorded if the subjects fail to remove their tails by this time. A single dosing procedure is used in all test sessions. Each experimental session begins with control determinations at each temperature. Subsequent tail withdrawal latencies are determined based on each experimental condition. The subjects are tested 1 to 2 times at three temperatures in a varying order, with approximately 1 to 2 min interval between tests. Experimental sessions are conducted once per week.

In this test Pharmaceutical Compounds are efficient in preventing or reversing carrageenan-induced hyperalgesia at a dosage in the range of from 0.01 μ Mole/kg to 1 mMole/kg.

Pharmaceutical Compounds are accordingly useful as bradykinin B₁ receptor antagonists, e.g. in the treatment of diseases and conditions in which B₁ receptor activation plays a role or is implicated. Such conditions include in particular pain, e.g. bone and joint pain (osteoarthritis), cancer pain, myofascial pain (muscular injury, fibromyalgia) and perioperative pain (general surgery, gynecologic surgery).

Pharmaceutical Compounds are particularly useful in the treatment or prevention of chronic pain, especially inflammatory, e.g. chronic inflammatory pain, inflammatory diseases for example inflammatory airways disease, e.g. COPD, or in asthma, rhinitis, inflammatory bowel disease, cystitis, e.g. interstitial cystitis, pancreatitis, uveitis, inflammatory skin disorders and rheumatoid arthritis.

Pharmaceutical Compounds are thus useful as bradykinin BK₁ receptor antagonists, e.g. for the treatment of pain of various genesis or aetiology and as anti-inflammatory and/or anti-oedemic agents for the treatment of inflammatory reactions, diseases or conditions, as well as for the treatment of allergic responses mediated by bradykinin. Having regard to their analgesic/anti-inflammatory profile they are useful for the treatment of inflammatory pain, for the treatment of hyperalgesia and, in particular, for the treatment of severe chronic pain. They are, for example, useful for the treatment of pain, inflammation and/or oedema consequential to trauma, e.g. associated with burns, sprains, fracture or the like, subsequent to surgical intervention, e.g. as post-operative analgesics, as well as for the treatment of inflammatory pain of diverse genesis, e.g. for the treatment of osteo and rheumatoid arthritis and rheumatic disease, teno-synovitis and gout. They are further suitable as analgesics for the treatment of pain associated with, e.g., angina, menstruation or cancer. As anti-inflammatory/anti-oedema agents, they are further useful, e.g., for the treatment of inflammatory skin disorders, for example psoriasis and eczema.

As bradykinin BK₁ receptor antagonists Pharmaceutical Compounds are also useful as smooth muscle relaxants, e.g. for the treatment of spasm of the gastro-intestinal tract or uterus, e.g. in the therapy of Crohn's disease, ulcerative colitis or pancreatitis.

Pharmaceutical Compounds are in particular useful as agents for the therapy of airways hyperreactivity and for the treatment of inflammatory events associated with airways disease, in particular asthma. In addition, Pharmaceutical Compounds may, for example, be used for the control, restriction or reversal of airways hyperreactivity in asthma.

Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic and, especially, extrinsic asthma. Thus, Pharmaceutical Compounds are useful for the treatment of allergic asthma, whether atopic (i.e. IgE-mediated) or non-atopic, as well as, for example, exercise induced asthma, occupational asthma, asthma induced following bacterial infection, other non-allergic asthmas and "wheezy-infant syndrome".

Efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack and by reduced requirement for other, symptomatic therapy, for example anti-inflammatory (e.g. corticosteroid) or bronchodilator (e.g. β_2 adrenergic) therapy.

Inflammatory or obstructive airways diseases to which the present invention is applicable further include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis.

Further inflammatory or obstructive airways diseases and conditions for which Pharmaceutical Compounds may be used include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), and bronchitis. Pharmaceutical Compounds may also be used for the treatment of allergic and vasomotor rhinitis.

In addition to the foregoing Pharmaceutical Compounds are also indicated for use in the therapy of septic shock, e.g. as anti-hypovolaemic and/or anti-hypotensive agents, in the treatment of inflammatory bowel disease cerebral oedema, headache, migraine and inflammatory skin disease such as eczema and psoriasis, and inflammatory disorders of the gut, e.g. irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystitis, e.g. interstitial cystitis, nephritis, uveitis.

For the above indications the appropriate dosage of Pharmaceutical Compounds will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated as well as the relative potency of the particular Pharmaceutical Compound employed. For example, the amount of active agent required may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect. In general, satisfactory results in animals are indicated to be obtained at daily dosages of from about 0.01 to about 20.0 mg/kg p.o. In humans, an indicated daily dosage is in the range of from about 0.7 to about 1400 mg/day p.o., e.g. from about 50 to 200 mg (70 kg man), conveniently administered once or in divided doses up to 4 x per day or in sustained release form. Oral dosage forms accordingly suitably comprise from about 1.75 or 2.0 to about 700 or 1400 mg Pharmaceutical Compound admixed with an appropriate pharmaceutically acceptable diluent or carrier therefor.

Pharmaceutical Compounds may alternatively be administered e.g. topically in the form of a cream, gel or the like for example for the treatment of conditions of the skin as hereinbefore described or by inhalation, e.g. in dry powder form, for example for the treatment of asthma.

Examples for compositions comprising Pharmaceutical Compound include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, e.g. cyclodextrin, a microemulsion and a suspension of, e.g. a micronized hydrochloride salt of a compound of formula IA in, e.g. aqueous methyl cellulose in the range of from 0.1 to 1 %, e.g. 0.5 %. The composition may be buffered to, e.g. a pH in the range of from 3.5 to 9.5, e.g. to pH 4.5, by a suitable buffer, e.g. malic acid.

Pharmaceutical Compounds are also useful as research chemicals.

In accordance with the foregoing the present invention also provides:

- (1) A pharmaceutical compound for use as a bradykinin BK_1 receptor antagonist, for example for use in any of the particular indications hereinbefore set forth;
- (2) A pharmaceutical composition comprising a pharmaceutical compound as under (1) as active ingredient together with a pharmaceutically acceptable diluent or carrier therefor;
- (2') A pharmaceutical composition for the treatment or prevention of a disease or condition in which bradykinin B_1 receptor activation plays a role or is implicated comprising a compound of formula IA and a carrier.
- (3) A method for the treatment of any of particular indication hereinbefore set forth in a subject in need thereof which comprises administering an effective amount of a pharmaceutical compound as under (1);
- (3') A method for treating or preventing a disease or condition in which bradykinin B_1 receptor activation plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula IA.

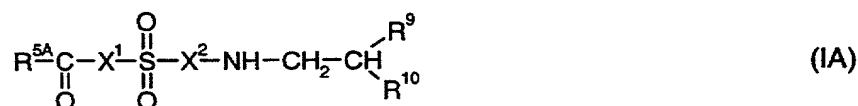
(4) Use of a compound of formula IA for the manufacture of a medicament for the treatment or prevention of a disease or condition in which bradykinin B₁ receptor activation plays a role or is implicated;

(5) A process for the preparation of a compound as under (1).

The preferred Pharmaceutical Compounds for use in accordance with the invention are those of Examples 1 and 2.

Claims

1. A compound of formula IA



wherein

$\text{R}^{5\text{A}}$ is $-\text{X}^{\text{A}}-\text{R}^{6\text{A}}$ or $-\text{N}(\text{R}^{7\text{A}})\text{R}^{8\text{A}}$, wherein

X^{A} is piperidinylene or piperazinylene,

$\text{R}^{6\text{A}}$ is H, C_1 - C_4 alkyl, C_3 - C_4 alkenyl, C_3 - C_4 alkinyl, C_1 - C_4 (alkoxyalkyl), C_1 - C_4 (carboxyalkyl), a C_5 - C_7 heterocyclic group or phenyl- C_1 - C_4 alkyl;

$\text{R}^{7\text{A}}$ is amino- C_2 - C_4 alkyl or mono- or di- $(\text{C}_1$ - C_5 alkyl)amino- C_2 - C_5 alkyl, and

$\text{R}^{8\text{A}}$ is H, C_1 - C_4 alkyl or has the meanings as given for $\text{R}^{7\text{A}}$;

X^1 is a divalent group of formula IA' $-(\text{CH}_2)_n-\text{X}^3-(\text{CH}_2)_m-\text{X}^4-\text{N}-$ wherein

n is zero or 1;

X^3 is CH or N;

(a) X^4 is a direct bond, $\text{R}^{3\text{A}}$ and $\text{R}^{4\text{A}}$ together are ethylene and m is 2; or

(b) X^4 is a direct bond, $\text{R}^{3\text{A}}$ is H, C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkinyl, C_7 - C_{10} aralkyl or C_6 - C_9 heteroaralkyl, $\text{R}^{4\text{A}}$ is H and m is 1 or 2 or 3; or

(c) X^4 is $-\text{CH}(\text{R}^{12})-$, $\text{R}^{3\text{A}}$ is H and $\text{R}^{4\text{A}}$ and R^{12} together are propylene and m is 1, or ethylene and m is 2;

X^2 is a divalent group of formula IA''  wherein

X^3 is CH or N; and

R^{11} is C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl or $-\text{NR}^{1\text{A}}\text{R}^{2\text{A}}$, wherein

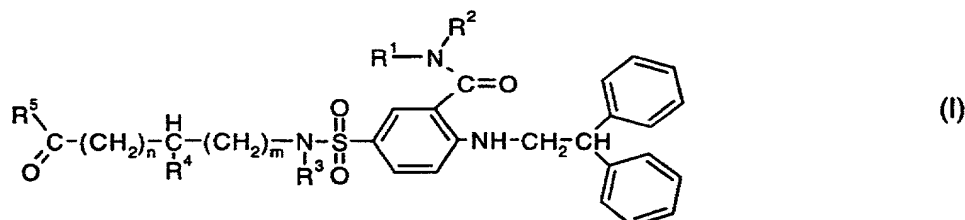
$\text{R}^{1\text{A}}$ and $\text{R}^{2\text{A}}$ independently are C_1 - C_4 alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring; and

R^9 and R^{10} independently are a phenyl or pyridine ring;

and salts thereof.

2. A 2-(2,2-diphenylethylamino)-5-(4-aminocarbonyl-piperidine-1-sulfonyl)-benzoic acid amide or -5-(aminocarbonyl-C₂-C₄alkyleneaminosulfonyl)-benzoic acid amide, or salt thereof.

3. A compound of formula I



wherein

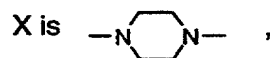
R¹ and R² independently are C₁-C₄alkyl or, together with the N-atom to which they are attached, represent a 5 to 7 membered heterocyclic ring;

(a) R³ and R⁴ together are ethylene and m is 2; or

(b) R³ is H, C₁-C₄alkyl, C₅-C₇cycloalkyl or phenyl-C₁-C₄alkyl, R⁴ is H and m is 1 or 2 or 3;

n is zero or 1; and

R⁵ is -X-R⁶ or -N(R⁷)R⁸, wherein



R⁶ is C₁-C₄alkyl, C₃-C₄alkenyl, C₃-C₄alkinyl, C₁-C₄(alkoxyalkyl), C₁-C₄(carboxyalkyl), a C₅-C₇heterocyclic group or phenyl-C₁-C₄alkyl;

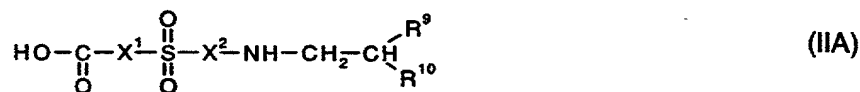
R⁷ is amino-C₂-C₄alkyl or mono- or di-(C₁-C₅alkyl)amino-C₂-C₅alkyl, and

R⁸ is H, C₁-C₄alkyl or has the meanings as given for R⁷;

and salts thereof.

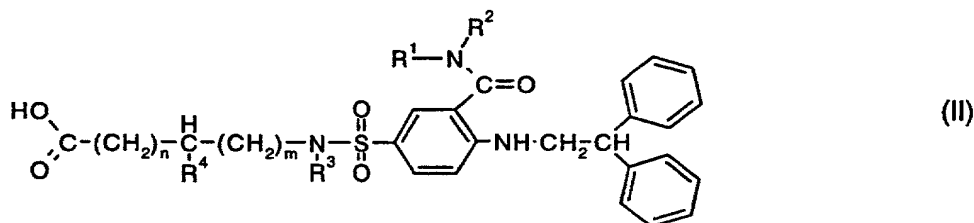
4. A compound according to claim 1 which is {2-(2,2-diphenyl-ethylamino)-5-[4-(4-isopropyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone, or {2-(2,2-diphenyl-ethylamino)-5-[4-(4-methyl-piperazine-1-carbonyl)-piperidine-1-sulfonyl]-phenyl}-morpholin-4-yl-methanone.

5. A process for the production of a compound of formula IA according to claim 1 which process comprises reacting a compound of formula IIA



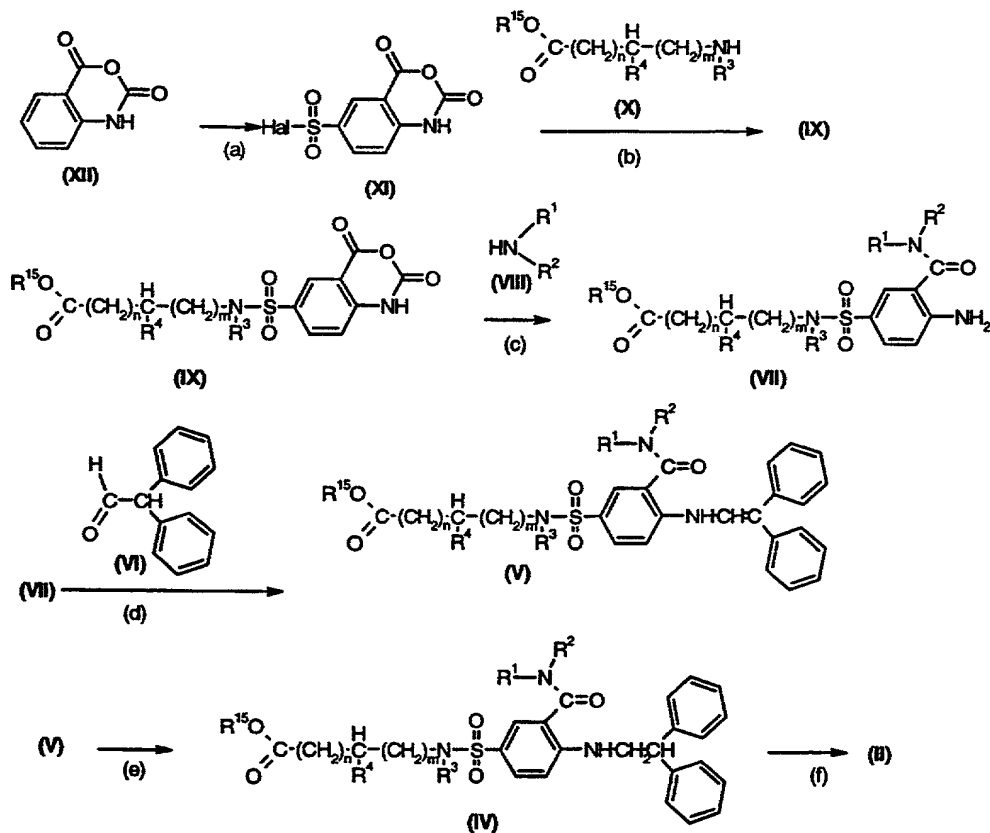
wherein X^1 , X^2 , R^9 and R^{10} have the meanings according to claim 1, with an amine and recovering the obtained compound in free or in salt form.

6. A process for the production of a compound of formula I according to claim 3, which process comprises reacting a compound of formula II



wherein R^1 , R^2 , R^3 , R^4 , m and n have the meanings according to claim 3, with an amine and recovering the obtained compound in free or in salt form.

7. A process for the production of a compound of formula II according to claim 6, which process comprises the steps as outlined in the following scheme:



wherein Hal is halogen, R¹⁵ is C₁-C₄alkyl, and R¹, R², R³, R⁴, m and n are as defined in claim 3.

8. A compound according to claim 1 for use in the treatment of the human or animal body.

9. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment or prevention of a disease or condition in which bradykinin B₁ receptor activation plays a role or is implicated.

10. A method for treating or preventing a disease or condition in which bradykinin B₁ receptor activation plays a role or is implicated comprising administering to a mammal in need thereof a therapeutically effective amount of a compound according to claim 1.

11. A pharmaceutical composition for the treatment or prevention of a diseases or condition in which bradykinin B₁ receptor activation plays a role or is implicated comprising a compound according to claim 1 and a carrier.

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Perry Court, Clerk Maxwell Road, Cambridge CB3 0RS
(GB). **RITCHIE, Timothy, John** [GB/GB]; 56 Burrard
Road, London NW6 1DD (GB). **WAYKOLE, Liladhar**
[US/US]; 11 Putters Road, Succasunna, NJ 07876 (US).

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(74) Agent: **BECKER, Konrad**; Novartis AG, Corporate In-
tellectual Property, Patent & Trademark Dept., CH-4002
Basel (CH).

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(71) Applicant (*for all designated States except AT, US*): **NO-
VARTIS AG** [CH/CH]; Schwarzwaldallee 215, CH-4058
Basel (CH).

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(71) Applicant (*for AT only*): **NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT MBH** [AT/AT];
Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

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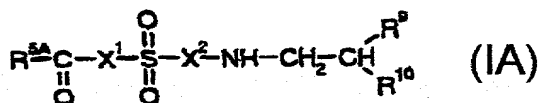
(75) Inventors/Applicants (*for US only*): **BRAIN, Christo-
pher, Thomas** [GB/GB]; 54 Cardinal's Gate, Wer-
rington, Peterborough, Cambridgeshire PE7 5A (GB).
CANTRELL, William [US/US]; 307 Laurel Ridge Drive,
San Antonio, TX 78253 (US). **CULSHAW, Andrew,
James** [GB/GB]; 10 Bracewell Avenue, Greenford, Mid-
dlesex UB6 7QU (GB). **DZIADULEWICZ, Edward,
Karol** [GB/GB]; 83 Wellsway, Bear Flat, Bath, Somerset
BA2 4RU (GB). **HART, Terance, William** [GB/GB]; 12

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(57) Abstract: Novel sulfonyl amine derivatives, of formula
(IA) processes for their production, their use as pharmaceuticals
and pharmaceutical compositions comprising them.

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DECLARATION AND POWER OF ATTORNEY FOR UNITED STATES PATENT APPLICATION

☒ Original ☐ Supplemental ☐ Substitute

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name, and

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a United States patent is sought on the invention entitled

BRADYKININ RECEPTOR ANTAGONISTS

the specification of which:

☐ is attached hereto.

☐ was filed on _____ as Application No. _____
(day/month/year)

and, if this box (☐) contains an *

☐ was amended on _____
(day/month/year)

☒ was filed as Patent Cooperation Treaty international Application No.

PCT/EP 00/05059 on **02.06.2000**
(day/month/year)

and, if this box (☐) contains an *

☐ entered the national stage in the United States and was accorded Application No. _____

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I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above and, if this application was filed as a Patent Cooperation Treaty international application, by any amendments made during the international stage (including any made under Patent Cooperation Treaty Rule 91, Article 19 and Article 34).

I acknowledge my duty to disclose all information which is known by me to be material to the patentability of this application as defined in 37 C.F.R. § 1.56.

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COUNTRY/REGION (OR P.C.T.)	APPLICATION No.	FILING DATE (day/month/year)	PRIORITY CLAIMED	
Great Britain	9913079.1	04.06.1999	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
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I hereby claim the benefit under 35 U.S.C. § 119 (e) of any United States provisional application(s) listed below:

APPLICATION NO.	FILING DATE (day/month/year)
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I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) listed below and under 35 U.S.C. §365(c) of any Patent Cooperation Treaty international application(s) designating the United States listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in said prior application(s) in the manner required by the first paragraph of 35 U.S.C. §112, I acknowledge my duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date(s) of the prior application(s) and the national or Patent Cooperation Treaty international filing date of this application:

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I hereby appoint the registered practitioners associated with Customer No. 001095, respectively and individually, as my attorneys and agents, with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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Full name of sole
or first joint inventor

Christopher Thomas BRAIN

Inventor's signature

Christopher Thomas Brain

Date

16 / 11 / 01

(day/month/year)

Residence

London, WC1E 6BN, Great Britain *CBK*

Citizenship

Great Britain

Post Office Address

The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain

IMPORTANT: Before this declaration is signed, the patent application (the specification, the claims and this declaration) must be read and understood by each person signing it, and no changes may be made in the application after this declaration has been signed.

William CANTRELL

William Condit

11 OCT, 2001
(day/month/year)

San Antonio TX 78253, USA TX

USA

**307 Laurel Ridge Drive
San Antonio TX 78253
USA**

Andrew James CULSHAW

Date _____

(day/month/year)

London, WC1E 6BN, Great Britain

Great Britain

**The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

Edward Karol DZIADULEWICZ

Date _____

(day/month/year)

London, WC1E 6BN, Great Britain

Great Britain

**The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

Full name of second
joint inventor, if any

William CANTRELL

Inventor's signature

Date

(day/month/year)

Residence

San Antonio TX 78253, USA

Citizenship

USA

Post Office Address

**307 Laurel Ridge Drive
San Antonio TX 78253
USA**

Full name of third
joint inventor, if any

Andrew James CULSHAW

Inventor's signature

Andrew James Culshaw

Date

19 / 11 / 2001

(day/month/year)

Residence

London, WC1E 6BN, Great Britain

GBX

Citizenship

Great Britain

Post Office Address

**The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

Full name of fourth
joint inventor, if any

Edward Karol DZIADULEWICZ

Inventor's signature

Edward Karol Dziadulewicz

Date

16 / 11 / 01

(day/month/year)

Residence

London, WC1E 6BN, Great Britain

GB

Citizenship

Great Britain

Post Office Address

**The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

500
Full name of fifth
joint inventor, if any

Terance William HART

Inventor's signature

Terance William Hart

Date

16/11/01
(day/month/year)

Residence

London, WC1E 6BN, Great Britain

Citizenship

Great Britain

Post Office Address

The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain

600
Full name of sixth
joint inventor, if any

Timothy John RITCHIE

Inventor's signature

Timothy John Ritchie

Date

16/11/01
(day/month/year)

Residence

London, WC1E 6BN, Great Britain

Citizenship

Great Britain

Post Office Address

The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain

Full name of seventh
joint inventor, if any

Liladhar WAYKOLE

Inventor's signature

Date

(day/month/year)

Residence

Succasunna, NJ 07876, USA

Citizenship

USA

Post Office Address

11 Putters Road
Succasunna, NJ 07876
USA

Full name of fifth
joint inventor, if any **Terance William HART**

Inventor's signature

Date

(day/month/year)

Residence **London, WC1E 6BN, Great Britain**

Citizenship **Great Britain**

Post Office Address **The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

Full name of sixth
joint inventor, if any **Timothy John RITCHIE**

Inventor's signature

Date

(day/month/year)

Residence **London, WC1E 6BN, Great Britain**

Citizenship **Great Britain**

Post Office Address **The Novartis Institute
for Medical Sciences
5 Gower Place
London, WC1E 6BN
Great Britain**

Full name of seventh
joint inventor, if any **Liladhar WAYKOLE**

Inventor's signature

Date

16-10-2001
(day/month/year)

Residence **Succasunna, NJ 07876, USA** **NJ**

Citizenship **USA**

Post Office Address **11 Putters Road
Succasunna, NJ 07876
USA**